WHAT WILL BE THE NEXT GREAT PLAGUES?

In May, 1997 a 3 year old boy was admitted to a Hongkong hospital with a serious febrile illness. He died a few days later: a lamentable event, but not one so rare as to make headlines. But this one did, for he was diagnosed as bearing a brand new strain of influenza. This reached world attention in November and December, when nearly a score of new cases appeared, all still in Hongkong: these numbered five more deaths with H5N1 influenza. With good reason, this episode evoked memories of pestilence sweeping across large sectors of the population.

Preceded by biblical and epic accounts, our earliest historical records attest how the human experience has been attended by great plagues: Athens in 430 BCE; Constantinople in 542 CE; in Europe from 1346 (the Black Death); and London 1664. These had achieved cataclysmic proportions, with anywhere from a tenth to a half of the people being afflicted. It has recently entered our consciences that the defeat of the native peoples of the Western Hemisphere was a comparable event, owing more to inadvertent measles and smallpox than to the cavalry or the martial skill of the Conquistadores. In more recent times, the (misnamed) Spanish Influenza of 1918 exacted a half-million American lives, and over 20 million worldwide.

Now, more than a century has elapsed since the foundations of scientific medicine were laid by Louis Pasteur and Robert Koch, culminating in the marvelous vaccines and wonder drug antibiotics of the 1950s. Smallpox has now been eradicated, and polio nearly so; and with antibiotics like penicillin and streptomycin, it appeared that most bacterial infections could be managed with a few pills. With that complacency, we have let down our guard -- and turned the major agenda of research and pharmaceutical development to other formidable challenges. These have been the diseases of the human constitution -- heart disease, cancer, psychiatric

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disorders -- not so easily attributable to external parasites. (Even that judgment may have to revised, with attributions of liver cancer to hepatitis B; of gastric ulcer, perhaps cancer to helicobacteria; and more controversially of heart disease to chlamydia infections, and of schizophrenia to slow neuroviruses.) These diseases are also correspondingly more difficult to study, since the target is intrinsic to our own bodies. In principle, it should be much easier to find drug chemicals that will selectively attack an alien bug, taking advantage of its alien physiology, than to locate modifiers of human metabolism without unwanted side effects. Noting the relationship of life styles, nutrition, and chemical pollution and abuse to these diseases, we have also become fixedly preoccupied with our chemical and physical environment, embracing the assumption that "artificial" is bad and "natural" is good, ignoring the perils that may beset us from natural predators.

That complacency, born out of pride in scientific, public health, and medical medical achievement, was rudely shaken by the AIDS pandemic, starting in the early 1980's. Here was a brand new disease, unknown to medical science, for which neither a chemical cure nor a preventive vaccine is yet in sight, even now. It is still spreading round the world, on the rise especially in Asia in varied antigenic types, even as its acceleration in this country is being tempered by education about safe sex -- or is it natural selection against the most profligate risk takers? It is also being tempered by the new protease-inhibitors, though few are optimistic that these will eventuate in long-term cures. They even convey what is called the "moral hazard" in the insurance lexicon: that some people will lessen their precautions so that the benefits of treatment will be neutralized. But along with AIDS, the last 20 years have seen the emergence or reemergence of dozens of other infections, making headlines by the month. One could make a long list, but enough to recite epithets like Ebola or Lassa fever;

Lyme; Legionnaires'; E. coli O-157; hantavirus; cholera O139; Cyclospora in raspberries; or Cryptosporidium in water supplies; and mad cows. Equally alarming is the growing array of microbial infections for which long-used antibiotics are no longer effective: drug-resistant pneumonia, tuberculosis, and have become global problems. Surgeons are apprehensive that common wound infections will again become untreatable, as in the pre-antibiotic era, and that many more patients will acquire infection in the hospital -- nosocomial infections -- as a byproduct of being treated in that environment.

None of these later comers has yet been a global scourge to match the 1918 flu, or HIV. They are lethal enough, but have been more or less limited in their territorial domain. However, they have opened our eyes to looming challenges of major pandemics in the domain of emerging infections. In this article, we try to assess which are the most grievous and problematic further risks; what is the biological and social matrix of emergence; what are the measures needed for individual and collective security.

Our perspectives are of course shaped by latter day assumptions of what we can expect by way of healthy life, expectations that have advanced enormously during this century. In the U.S., mortality from AIDS today has (we hope) peaked at about 17 per 100,000 annually -- a bit less than succumbed to syphilis each year between 1910 and 1940; and the same for diphtheria and typhoid fever between 1900 and 1920. The latter three diseases reflect a glorious triumph in the development and use of antibiotics and vaccines, and of sanitized water supplies. The death rate from the Spanish flu, during its brief swath across the U.S. was nearly 600 per 100,000. It came and went without the benefit of any expertise about cure: it is simplest to say that it burned itself out when it no longer find naive, non-immune hosts, almost 99% of humans having been exposed and survived.

What lies ahead?

The world of microbes is so diverse, so complex -- new pathogens might arise from any of a thousand extant species, and their unceasing evolution into new ones. "Professional" pathogens have evolved many specific adaptations to life in the host, circumventing our immune systems (and latterly the drugs we invent), assuring their transmittal from one victim to another. New pathogens are then most likely to emerge either (a) as further refinements of diseases already present in the human, or (b) crossovers from animal diseases --zoonoses. The most striking and well-documented examples of (a) are the drug-resistant variants; for (b) we can cite plague, yellow fever, hantavirus, and very likely HIV. Rarely, as with Legionnaires', we see a bacterium whose normal habitat is in the soil, whose manifestation as human disease is incidental to its life cycle -- these would require a major evolutionary jump to become readily transmissible from person to person, and therefore a pandemic threat.

Although we already have a sizeable catalogue, new zoonoses may yet be discovered, though we will eventually exhaust the reservoir of viruses infesting monkeys and rodents at forest margins. We should be especially cautious not to ease the path for, say, a monkey virus by transplanting organs into human hosts, particularly humans whose immune system is already compromised. When such experiments are done, as has been projected for treating AIDS, they should be governed by meticulous study and monitoring of both the transplant tissue and of the receiving host, lest they be the seat of brand new zoonoses. We were unable to predict AIDS; and we must just leave open the prospects of further surprises like that.

As to human-based diseases, malaria and tuberculosis are already grievously prevalent, and preventive vaccines for either have had limited success. The causative agents are a protozoan

and a bacterium respectively. In broad theoretical terms, it should not be that difficult to devise new chemical treatments, new antibiotics: most specialists feel that will be a direct function of the level of research invested in their discovery and development. The markets for these drugs are skewed to the developed world, well able to pay for new technology. Accordingly, the private sector pharmaceutical industry has posted notable successes in responding to those markets. But it has largely ignored the diseases most prevalent in the less developed countries (notably malaria and tuberculosis). Without a marked acceleration of governmental cooperation and funding for research on drugs and vaccines for these "third world diseases", they are likely to exact an ever increasing toll on human life and the global economy. Eventually that disease burden will also cross the oceans in one form or another, as was the case for AIDS. The technical challenges will be boosted by the exciting prospect of genomics, the complete decoding of the genetic blueprints for each of a dozen, we hope eventually hundreds of strains of pathogenic microbes. The gene studies already point to unique features of each pathogen that should be soft spots for chemical targetting.

Viruses are another matter, rarely do we have very effective antiviral chemicals. We ask, what are viruses? which ones are prevalent in humans, perhaps most likely to evolve further, and grow out of control?

Viruses are autonomous genetic particles that reproduce themselves like germs or genes do, but only within the cells they infect. They have evolved their own mechanisms of recognizing host cells, penetrating the cell membranes, and exploiting the cells' metabolism for their own benefit. They then also have specialized mechanisms to exit the cell, and go on to infect new ones. Within the host body they face many hostile defenses, notably a fine-tuned immune system. They must also have evolved strategies to penetrate the host organism,

to leave it, and to survive the intervening journey. That portal to portal may be body fluids (transfusion; sexual contact; contaminated needles, or a mosquito bite); excreta contaminating ingested water or food or on the hands of personal contacts; or airborne droplets (coughs and sneezes). The unbroken skin is an impermeable barrier, except to vectors like ticks and mosquitoes, rabid dog bites, or worm larvae (swimmers' itch). The coughs and sneezes associated with respiratory viruses may well be an evolved trait of the virus to promote their spread. Many of the other symptoms are byproducts of the host's defensive pharmacopeia, invoked to try to shed the virus. Some viruses have learned to manipulate those defensive reactions to their own benefit: for example, the rotaviruses that cause severe diarrhea benefit from that symptom by the facilitated spread of infection, though the host may benefit by evacuating the offending virus particles.

We can characterize viruses as containing the same sort of DNA and RNA as is used in our own cellular reproduction and physiology: this bedevils us in trying to find therapeutic remedies safe for the host. Furthermore, we really have no firm evidence of how the scores of known viruses ultimately evolved; though it is safe to assume that they were rogue escapees from the normal cell, much as cancers are rogue cells that have shaken off the regulatory discipline of the integrated organism. (We are a community of cells evolved for exquisite cooperation: skin cells normally scale and die to give the body a protective coat; muscles labor hard to pump the blood, seize and grind the food, move us over the ground. If any of these cells starts to multiply out of control, following its own evolutionary course, we have a cancer).

These insights about viruses are complicated by the learned habit of many viruses to have intercourse with the DNA of the host cell's chromosome: in effect to enter it, and for many

generations to simulate the normal genes therein. Later on they may be re-mobilized as autonomous particles again. The retroviruses, of which HIV is the most notorious example, are especially prone to this game. Many hundreds of such viruses are historically integrated into the normal human genome. There are odd examples of cancer or other disease emerging from such remobilized viruses in animals. Their biological or pathological significance in the human is for now quite mysterious. It can be said that the propensity for HIV virus to burrow into the chromosomes of some classes of white cells is a very discouraging portent against the likelihood of effecting total cures of HIV disease once it is established.

All things considered, the likeliest manifest candidate for the next plague would be a virus of high lethality that learns a new mode of spread, or a highly communicable virus that turns more vicious. In the former category might stand an HIV that mutated to a pneumonic form, one that like pneumonia is communicated by sneezes and coughs, then penetrating the lungs. Something like this did happen in the great plague of the 14th Century. This was originally the "bubonic plague", the "buboes" being huge skin pustules. But as the plague progressed, there were more and more cases of pneumonic spread, direct from human to human, bypassing the fleas and rats that were the reservoirs for the bubonic form.

For HIV, so far there is not a shred of evidence for this eventuality; though there has been almost no direct research on the actual barriers to pneumonic transmission to explain why we don't see it. If this ever occurred, it might be in conjunction with other respiratory infections that might beset persons with HIV or their contacts. Someone whose lungs were already inflamed with other infections should be more vulnerable to the intake of an HIV particle; or conversely more likely to be coughing these up. It is already established that people with HIV are more amenable to infection with tuberculosis.

In scanning for other candidates for the next great plagues, an intermediate category might be hepatitis A, which is communicated by excreta with very high efficiency, and has therefore infected hundreds of millions of people. It can be lethal, but the severest manifestations occur rather infrequently in its present form. Fortunately, there is an excellent vaccine -- including improved versions using recombinant DNA / genetic engineering technology, and prophylactic vaccination is ready to afford great relief at both an individual and a public health level.

The exemplar of the last category is the influenza virus, which afflicts a substantial percentage of the population every winter season. It is subject to frequent mutational changes, which alter its antigenic composition, so that each year calls for a fresh updating of the vaccines. Influenza strains circulate through wild birds, including migratory ducks and geese; each year's hatch provides new non-immune hosts. These are typically quite mild in their disease impact, and the bird flu may go unnoticed between episodes when it mutates to more devastatingly bird-killing varieties. Influenza in the human is too often underestimated: it can account for 10% of overall mortality in epidemic seasons, though most often this is in people who are already debilitated by other disease. Swine may be more readily accomodating to both bird and human strains of flu, and thus may be the mixing vessel where new recombinant flu strains are generated, from time to time conferring antigenic uniqueness or higher lethality on human-adapted and -transmissible varieties. This has been the consensual model of what happened in 1918 -- almost certainly in the American mid-West rather than in Spain. South China is now believed to be the ecologically favored site for this evolution in the contemporary world. The Hongkong flu of 1968 is attributed that that scenario. While, might one say, not to be sneezed at, the pandemic disease it engendered was hardly comparable to the 1918 strain. But influenza specialists are almost unanimous in the

conviction that a recurrence of a strain like 1918 is virtually inevitable, as the basic mechanisms to produce it are rife. If anything the patterns of global air traffic today would ensure a much more rapid spread: over a million passengers daily board an aircraft for an international destination!

Pneumonia is one of the common complications of the flu; and arguably it might be managed more successfully in today's hospitals than happened in 1918. Treatment of secondary bacterial infections with the antibiotics now available could certainly lend additional hope for cure. Unfortunately, drug-resistance is also spreading rapidly among many respiratory bacteria; and even today, influenzal pneumonia accounts for tens of thousands of deaths annually. In the course of a major pandemic, our hospital facilities would be overwhelmed by the case loads: so the ideal level of supportive care could not be had.

Against this historical backdrop, the sudden appearance of the new type of influenza in Hongkong, A-H5N1, was a source of consternation with the very first fatal case in May 1997. Similar strains were known to be circulating in birds, and the authorities soon turned a watchful eye. The 17 new cases in November and December were enough to trigger a global alert, and strenuous collaborative efforts embracing experts from the US Centers for Disease Control laboratories in Atlanta. Extensive surveillance and epidemiological study pointed to direct contact with infected chickens as the main, if not only, source of contagion. There was no clear evidence of person to person spread (notorious for standard human flu), and the number of new cases did not escalate. At the end of December, the Hongkong authorities decided to sacrifice the entire flock of chickens in the territory as a precaution against further cases. They were especially concerned to wipe out the H5N1 bird flu before the arrival of the seasonal human flu, peaking in March. That might encourage mixing of flu strains, the the

generation of still more lethal variants.

Since the sacrifice of the chickens, and from January through end-March 1998 (the writing of this article), there have been no new cases. 6 deaths out of 18 cases speaks to a highly lethal variant of the flu, once it is established in the human; but one not readily transmitted. Since hundreds of thousands of travellers have transitted Hongkong, and flown everywhere on the globe, that is indeed fortunate. All present indications are that humanity experienced a close call; and we are all in debt to the Hongkong health authorities for the professional and responsible way in which they pursued the task.

The latest word from the CDC is that the birds were experiencing not one, but two similar bird-lethal viruses, which would complicate the prospective vaccines. We cannot just turn our backs on the situation; as the biological cauldron churning out new strains continues to function. Government agencies, medical centers and the vaccine industry have been conferring to generate better-founded plans for dealing with future epidemics.

As enunciated by Drs. Peter Patriarca and Nancy Cox, from the FDA and CDC respectively, the plan focuses on six major areas:

(1) improvements in ongoing virologic and disease-based surveillance systems;

(2) vaccination of high-priority target groups, and, given sufficient vaccine supplies, the entire US population;

(3) indemnification programs for vaccine manufacturers and health care providers;

These would provide a "no-fault insurance" protection to all sides in the event of mishaps following vaccination, provided federal standards had been met.

(4) research to improve detection of new variants and to accelerate the availability of existing

and novel vaccines and antiviral agents;

(5) integrated, multicomponent communication systems for rapid information dissemination and exchange; and

(6) emergency preparedness plans to provide for adequate medical care and maintenance of essential community services.

Such planning is indispensable if today's global village is to have any chance of coping with these new plagues. It has to be said that existing vaccines are only barely satisfactory, and current methods for their production are pinned down by logistical issues like the availability of fertile hens' eggs of proven breeds. Not to mention the time that can be consumed in verifying new flu types, the need to proceed with crash production, and the habituation of the viruses for practicable growth in eggs. The H5N1 was so bird-lethal that inoculated eggs were killed before they could deliver much of a yield of virus for making vaccine. These problems are being ironed out right now.

The situation is hardly better for the chemotherapeutic treatment of the flu. An antiviral drug, rimantadine, was developed in the 1980's. It can be used to mitigate symptoms, but it is sufficiently toxic to raise questions about its use in mass prophylaxis; and it will almost certainly promptly select for genetic resistance to the drug. Research investment to deal with flu has been hampered by the misperception that it is just a bad cold, though research in this area is beginning to receive the attention it deserves. Hopefully, the six fatal encounters in Hongkong are a warning that, with our current breathing spell, may be heeded to universal benefit. That will require the concurrence of professional judgement, industrial and governmental policy-makers, and an informed and interested public.